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EDITORIAL

Stimulating Dialogue Through Treatment of Poststroke Aphasia With Transcranial Direct Current Stimulation

Steven C. Cramer, MD, MMSc

Stroke remains a leading cause of human disability. Important gains have been realized in the setting of acute ischemic stroke, where thrombolytic and catheter-based reperfusion therapies can substantially improve long-term behavioral outcomes. However, most patients with a new stroke are not eligible for such therapies because of delays in diagnosis or hemorrhagic etiology, for example, and many who are treated nonetheless have substantial long-term disability. Additional classes of poststroke therapy are needed.

An emerging branch of stroke therapeutics targets neural repair. Such restorative therapies are introduced after stroke-related injury is fixed and therefore do not aim to modify the initial insult. Instead, the strategy is to improve outcomes by promoting favorable clinical neuroplasticity within surviving neural elements.¹ Many categories of brain repair therapy are under study, including small molecules, growth factors, monoclonal antibodies, cells, activity-based therapies, telerehabilitation, and brain stimulation.² Several forms of brain stimulation have been advanced. An advantage of this approach, compared with systemic administration of a drug, is reduced toxicity given that trillions of cells outside the brain are not exposed. Transcranial direct current stimulation (tDCS) has the additional advantage that it is noninvasive, passing direct current through the scalp/skull to the brain, producing a subthreshold modulation of resting membrane potentials, and thereby modifying the function of distributed brain networks.

In the current issue of *JAMA Neurology*, Fridriksson et al³ examined the effects of tDCS on language function in patients with chronic stroke and aphasia. These authors performed a double-blinded, prospective, randomized, controlled clinical trial at 2 US sites. Enrolled individuals had a history of a single ischemic stroke in the dominant left hemisphere at least 6 months prior. At the time of enrollment, study participants had aphasia that was neither too severe (participants had to score >65% accuracy on an object naming test) nor too mild (score on the Philadelphia Naming Test needed to be <80%). Individuals were randomized to speech therapy accompanied by either active or sham tDCS that was applied during the therapy. The primary end point was the change in the number of correctly named common objects from pretreatment to 1-week posttreatment.

In both study groups, speech therapy consisted of 15 outpatient sessions of 45 minutes' duration over a 3-week period. Individuals in the active tDCS group also received 1 mA

of anodal tDCS, whereby two 5 × 5 cm sponges were placed, 1 of which (the anode) was on the left scalp over a targeted cortical region and the other of which (the cathode) was on the right supraorbital scalp; in general, anodal tDCS increases cortical excitability.⁴ The targeted cortical region was identified by a functional magnetic resonance imaging scan obtained at baseline, ensuring that stimulation was centered over a functionally intact left temporal lobe region, and underscoring the utility of using a measure of brain function to direct details of a restorative therapy for individual patients.⁵

The 2 groups were generally well matched at baseline, although the active tDCS group tended to have better aphasia scores at baseline (results were little changed when adjusting for this). The mean (SD) age of all individuals was 60 (10) years. Of 74 enrolled patients, 52 (70%) were men, and the individuals had a mean (SD) of 15 (2) years of education. Depression was uncommon. Many types of aphasia were present, the most common being Broca aphasia. Treatment was well tolerated, consistent with the overall published experience with tDCS: tDCS up to 4 mA appears to be safe with no serious adverse events and no tDCS-induced seizures across thousands of sessions in healthy individuals, individuals with a neurologic diagnosis, or individuals with a psychiatric diagnosis.⁶

The main study finding was that the mean (SE) treatment-related change in correct object naming was 13.9 (2.4) words for active tDCS combined with speech therapy and 8.2 (2.2) words for sham tDCS combined with speech therapy. This represents an absolute increase of 5.7 words (95% CI, −0.9 to 12.3) and a relative increase of 70% for active tDCS compared with sham tDCS. The study used a futility design, whereby the null hypothesis assumed a benefit for active compared with sham tDCS, while the alternative hypothesis assumed no difference between active and sham tDCS. The *P* value for the futility hypothesis was .90.

What is the meaning of a futility hypothesis *P* value of .90? This indicates that the study failed to reject the null hypothesis (ie, the study did not provide evidence that anodal tDCS as used herein is futile) and so indicates that further evaluation of the active intervention is warranted. Futility design was born out of oncology research and was developed to reject candidate therapies with a low probability of success. Members of the current study team³ were among those who pioneered this approach in neurologic studies.⁷ Futility trials of putative therapeutic agents may be of particular value when the target disease is heterogeneous, has a protracted or unpredictable course, or lacks straightforward and widely used outcome measures.⁸ In a typical trial focused on comparative ef-

ficacy, the null hypothesis states that the active and control interventions have equal efficacy and is rejected if the primary outcome measure is significantly different between the 2 groups. However, in a futility trial, the null hypothesis is that the active intervention will improve the outcome relative to control by a prestated margin: if the active treatment does not achieve this, the null hypothesis is rejected and the treatment is deemed futile; if the active treatment does achieve this, the null hypothesis is not rejected and the treatment is declared nonfutile and thus worthy of further investigation.⁸ In a futility study, data can reject the null hypothesis but not confirm it; failure to reject the null hypothesis in a futility study is not tantamount to assigning superiority of the active treatment relative to control. Instead, failure to reject the null hypothesis suggests that it is logical to proceed with further evaluation of the active treatment.⁹

Any follow-up study to the current trial might be informed by understanding which patient features predict treatment efficacy. Response to restorative therapies after stroke is often highly variable, particularly for tDCS,¹⁰ in part because of large interindividual differences in stroke-related injury and in poststroke plasticity. Not surprisingly, treatment efforts to promote brain plasticity after stroke produce inconsistent results. Biomarkers have the potential to distinguish patient subgroups and thus identify persons who are likely to respond favorably to a given restorative therapy.¹¹ In the study by Fridriksson et al,³ baseline aphasia severity predicted the extent of treatment-related gains. Studies from a number of groups have consistently found that measures of neural injury and neural function can substantially improve on the predictive value provided by behavioral examination and so are useful for patient selection and stratification in restorative stroke trials.¹²⁻¹⁴

Any future studies of tDCS combined with speech therapy to improve poststroke aphasia will need to consider several key questions. Which population should be enrolled? In studies of restorative therapies after stroke, there is a tension between enrolling a narrowly defined population to reduce interindi-

vidual variance and so retain sufficient power to detect a true treatment effect vs enrolling a broad population to insure that results will substantially generalize. Which dose should be studied? The current choice for therapy duration, 3 weeks, was selected to match a typical dose of outpatient language therapy for chronic aphasia in the United States.³ The question arises whether a longer duration of treatment might produce larger gains. For how long should patients be assessed after therapy? Another tension in studies of restorative therapies after stroke is duration of follow-up: short durations are more reflective of actual treatment effects but have lower effect because any benefits observed may not be lasting. Longer durations of follow-up can detect lasting gains but often reflect additional influences, such as new onset depression or new stroke, that are unrelated to the specific hypothesis under study.

What does the ability to name 13.9 more objects mean in real life? If you are trying to order lunch or select a grandchild's birthday present, it can mean the world. If you are litigating a criminal case, it is likely insufficient. For most patients, this improvement may be clinically important. Indeed Fridriksson et al³ note that "even 1 to 2 words' improvement could be meaningful to some patients who have very limited speech output." Likely, the global outcome measures found useful in acute stroke studies, such as the modified Rankin Scale, would be insensitive to most behavioral gains provided by the current intervention, underscoring the importance of modality-specific end points in restorative stroke trials.¹⁵

The study by Fridriksson et al³ thus can be said to provide no evidence that anodal tDCS as used herein and combined with speech therapy is futile. The authors conclude, rightly, that these data provide motivation to proceed with further study of the effect of this form of active tDCS combined with speech therapy on aphasia outcomes poststroke. Over time, identification of the ideal therapy intensity and duration, as well as target population, offers hope that language function can be substantially improved in individuals with poststroke aphasia.

ARTICLE INFORMATION

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